Case Report

Pulmonary Alveolar Proteinosis: Case Report of Rare Diffuse Lung Disorder in Pediatric Age Group

Vipulkumar Gandhi, Shashank Kadam
Department of Pediatrics, K.E.M. Hospital, Pune, Maharashtra, India

Abstract

Nonspecific symptoms and variable clinical course are a few of the hurdles in diagnosing pulmonary alveolar proteinosis (PAP). Lack of accessible health care and efficient health infrastructure, including diagnostic and treatment facilities, are the major challenges for early detection and prompt management of PAP in developing countries such as India. A 6-month-old child was brought to the tertiary health care center for cough, dyspnea, and intermittent fever. The history of third-degree consanguineous parents was evident. The patient had a history of evolving respiratory complaints at the age of 4 months, for which she was hospitalized for 12 days. There was a relapse of similar symptoms within 2 weeks of discharge and required readmission. The patient was cyanosed with signs of severe respiratory distress. Chest X-ray revealed bilateral diffuse alveolar infiltration. High-resolution computed tomography imaging showed diffuse interstitial thickening with adjacent ground-glass opacities along with crazy-pavement appearance involving both lungs. With flexible bronchoscopy, bronchoalveolar lavage (BAL) was performed. Congenital PAP was confirmed with periodic acid–Schiff -positive proteinaceous extracellular globules on smear. The child was intubated and mechanically ventilated during a hospital stay to treat uncontrollable respiratory failure. The child succumbed on the 28th day of admission despite repeated therapeutic BAL procedures and systemic corticosteroids. The possibility of missed/delayed diagnosis of PAP is widespread in resource-limited health-care settings. Postnatal onset of PAP should be suspected in every child with chronic respiratory distress and failure to thrive with diffuse alveolar infiltrates.

Keywords: Bronchoalveolar lavage, diffuse alveolar infiltrate, pulmonary alveolar proteinosis

Introduction

Pulmonary alveolar proteinosis (PAP) is one of the rare causes of restrictive lung pathology in children. It is characterized by alveolar accumulation of proteins and lipids due to defective surfactant clearance by alveolar macrophages.[1] Congenital PAP is caused by the genetic mutations observed in one of the numerous genes involved in the synthesis and functioning of pulmonary surfactant.[2] The diagnosis is done using a combination of clinical features, radio-imaging, bronchoalveolar lavage (BAL), and lung biopsy. Other tests such as genetic analysis and serum anti-granulocyte-macrophage colony-stimulating factor (GM-CSF) antibodies are helpful for confirmation. The disease progression is typically insidious with a varying presentation and nonspecific symptoms, which may delay the diagnosis of PAP by months to years.[3] In this study, one case of confirmed PAP is reported. The epidemiological aspects, symptomatology, diagnostic, and management modalities were all considered.

Access this article online

Quick Response Code:

Website: www.ijrc.in

DOI: 10.4103/ijrc.ijrc_130_21

Case Report

A 6-month-old female child was brought to the tertiary health-care facility of Western India by parents with complaints of cough, breathlessness associated with mild-grade fever in the past 4 days. Obstetric history revealed full-term normal delivery with no significant perinatal complications. An infant was the first child of third-degree consanguineous marriage without any associated familial respiratory illness. The child had a similar history of respiratory complaints at the age of 4 months, which required hospitalization for 12 days. However, symptoms relapsed within 2 weeks of discharge and required

Address for correspondence: Dr. Vipulkumar Gandhi, Department of Pediatrics, K.E.M. Hospital, Pune - 411 011, Maharashtra, India.
E-mail: v.2.gandhi@gmail.com

How to cite this article: Gandhi V, Kadam S. Pulmonary alveolar proteinosis: Case report of rare diffuse lung disorder in pediatric age group. Indian J Respir Care 2022;11:169-72.

Received: 25-10-2021 **Revised:** 02-12-2021
Accepted: 03-12-2021 **Published:** 08-04-2022

readmission for another week. The child appeared stunted and failure-to-thrive with a weight of 4.3 kg on admission.

Physical examination revealed tachypnea with a baseline respiratory rate of 70–80 breaths/min. The child was cyanosed with evident signs of severe respiratory distress. Lung auscultation revealed bilateral coarse crepitations. The child was markedly hypoxemic (pH 7.38, PCO_2 33 mmHg, PO_2 49 mmHg, SaO_2 86%) and was initially stabilized on a high-flow nasal cannula with a 40% oxygen supplement. Apart from marginal leukocytosis (TLC: 12700/cmm), other blood workups were normal on admission. Chest radiograph delineated bilateral diffuse alveolar infiltration with air bronchogram. High-resolution computed tomography (HRCT) imaging revealed diffuse interstitial thickening with adjacent ground-glass opacities along with crazy pavement appearance involving both lungs [Figures 1 and 2]. Abdominal ultrasonography documented diffuse hepatomegaly with no other abnormalities. Echocardiography, immunological profile including human immunodeficiency virus and cytomegalovirus status, and serum immunoglobulin levels were within the normal limits. Despite detailed investigations, no underlying respiratory fungal, viral, and bacterial pathogens were identified.

Considering noninfective chronic respiratory disorder, the sweat--chloride test was documented. A negative sweat-chloride test excluded the possibility of cystic fibrosis. Characteristic radio-imaging findings with negative infective/metabolic etiology, PAP was suspected. The child underwent flexible bronchoscopy, and BAL was performed. Microscopic evaluation of BAL fluid was sterile and showed periodic acid–Schiff stain positive proteinaceous extracellular globules on smear, confirming the diagnosis of congenital PAP [Figures 3 and 4]. On the 23rd day of admission, her respiratory failure worsened, for which she was intubated and supported with mechanical ventilation. She required multiple therapeutic BALs and systemic steroids as anti-inflammatory measures. However, despite all supportive measures child could not survive and succumbed on the 28th day of admission.

Discussion

The incidence of PAP in the pediatric age group is very rare,

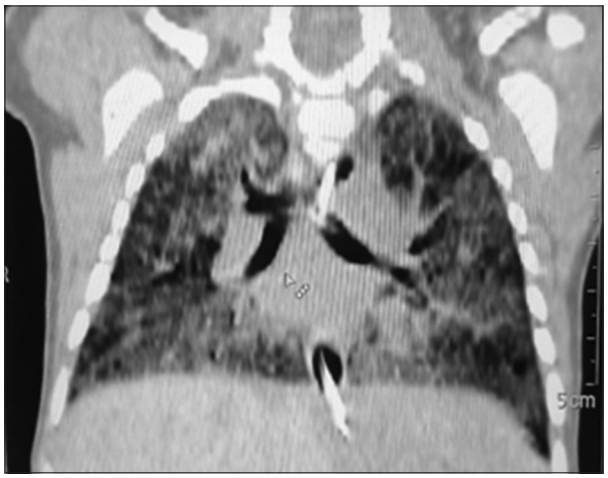

Figure 1: Coronal section

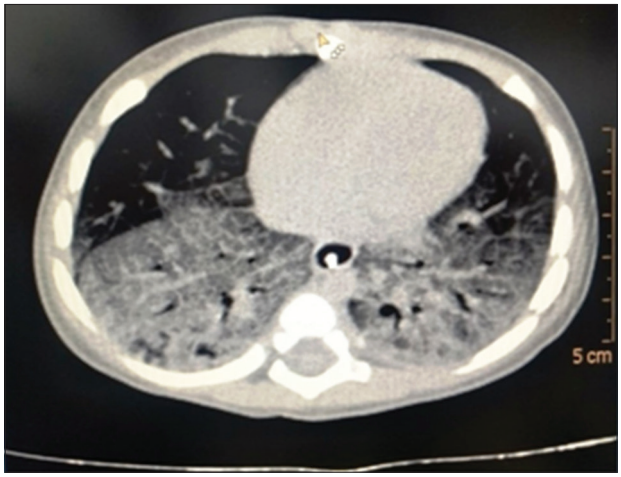

Figure 2: Axial section

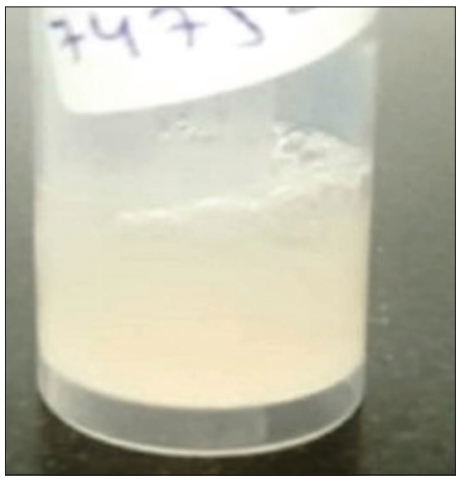

Figure 3: Color of bronchoalveolar lavage sample

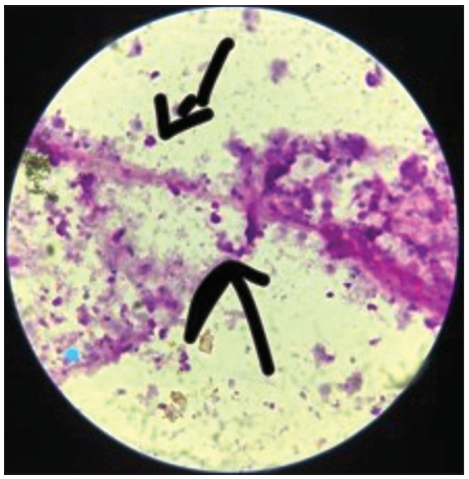

Figure 4: Bronchoalveolar lavage positive with periodic acid–Schiff staining on microscopy

and only limited cases have been reported in the literature.[4] The disease is polymorphic with multifactorial etiology. In this case, the child presented with cough, fever, and progressive dyspnea, comparable with other case series.[3,4] However, weight loss, hemoptysis, and chest pain have also been documented in the literature.[5] Due to nonspecific symptomatology, variation in severity of disease, and physicians' unfamiliarity, the diagnosis of PAP can be easily delayed or missed.[6] The literature reported a mean of 4.5 months' delay between presentation and diagnosis of a patient with PAP. In our case, an approximate duration between the 1st clinical manifestations to diagnosis was 2 months. This could be attributed to complexity in the clinical course of the disease, poor access to diagnostic modalities, etc. Clinical diagnostic and management modalities are summarized in Table 1.

Table 1: Lessons learnt

Diagnosis	Radiological findings, genetic testing, antibodies (anti-GM-CSF), bronchoscopy, lung biopsy
Treatment	Anti-inflammatory therapy: Corticosteroids, hydroxychloroquine, and azithromycin, etc. Whole lung lavage Recombinant GM-CSF Immunomodulatory therapies - Rituximab and plasmapheresis Lung transplantation
Prognosis	SFTPB or ABCA3 mutations in neonates with respiratory failure are usually fatal without lung transplantation Children with hereditary PAP (due to mutations in the GM-CSF receptor) often have severe, progressive lung disease, but unlike the congenital forms of the disease, they may respond to WLL

GM-CSF: Granulocyte macrophage colony-stimulating factor, PAP: Pulmonary alveolar proteinosis, WLL: Whole lung lavage

Table 2: Pediatric pulmonary alveolar proteinosis review of studies

Authors	Year of publication	*n*	Mean age	Sex	Consanguinity of parents	Predominant radiological finding	Other diagnostic modalities	Treatment	Outcome
Garg *et al.*[8]	2009	1	4 months	Male	No	Diffuse opacification with air bronchogram in bilateral lung fields except in the right middle lobe	Chest CT scan Flexible bronchoscopy BAL OLB	HOT Surfactants	Death
Verhasselt-Crinquette *et al.*[6]	2009	2	2 months	Male	No	Bilateral alveolar syndrome	Lung biopsy Echocardiography Immunohistochemistry BAL RT-PCR	O^2 therapy Supportive treatment	Death
Tabatabaei *et al.*[2]	2010	8	28 months	Males - 4 Females - 4	Present with 5 cases	Diffuse alveolar infiltrates	Chest CT scan OLB Echocardiography	WLL CPB GM-CSF Antibiotics O^2 therapy	100% survival for 2 cases and death for 4 cases
Hammami S *et al.*[7]	2013	1	3 months	Male	Present	Diffuse alveolar infiltrates	Chest CT scan Echocardiography Liver and renal function tests BAL	Three lung lavages	Death
Al-Haidary *et al.*[9]	2017	1	5 years	Male	No	Widespread bilateral airspace disease	CT scan of chest BAL	Whole lung lavage	100% survival
Iyengar and Reddy[1]	2018	2	6 months	Male	No	Hyperinflated lung fields with bilateral nonhomogeneous opacities	HRCT Lung biopsy, BAL, blood gas analysis	HOT oral prednisolone hydroxychloroquine Ventilator support	100% survival for first case and lost to follow up for 2nd case
Zhang *et al.*[10]	2020	1	9 months	Male	No	Bilateral ground-glass density images in lungs	Chest CT scan Lung biopsy Bronchoscopy with BAL	Imipenem, sulperazone Erythromycin Methylprednisolone Human immunoglobulins	100% survival

CT: Computed tomography, HRCT: High-resolution CT, HOT: Home oxygen therapy, *n*: Number of cases, OLB: Open lung biopsy, WLL: Whole Lung Lavage, CPB: Cardiopulmonary Bypass, GM-CSF: Granulocyte macrophage colony-stimulating factor, BAL: Bronchoalveolar lavage, RT-PCR: Reverse transcription–polymerase chain reaction

Late or undetected PAP diagnosis may be possible in resource-limited health care set up like India, where there is a scarcity of diagnostic (BAL fluid examination, genetic workup, etc.) and treatment facilities, especially in rural and marginalized sectors. The characteristic radiological appearance of PAP is bilateral, symmetric, and perihilar airspace consolidation in a bat-wing distribution.[7-9] In our study, the radiological finding suggested diffuse alveolar infiltration, which was consistent with previous studies.[1,2] However, few cases have also reported interstitial and nodular patterns.[7] An important finding of the present study was the association between PAP and consanguinity. In this case, the child had a history of third-degree consanguineous parents. Table 2 shows that out of 17 cases, 6 (35.29%) had a positive history of consanguinity, which underlines the importance of "Genetic Diagnostics" in detecting SP and GM-CSF receptor mutations of PAP. Unfortunately, due to financial constraints in our study, underlying genetic mutation workup could not be implemented, which is the case with most of the Indian reported studies.

In our case, three treatment modalities were implemented: BAL, mechanical ventilation, and corticosteroids. Similarly, BAL was also tried as the principal mode of management of PAP in other studies.[2,6,7,9] However, the utility of whole lung lavage (WLL) is limited due to technical challenges related to the application of large endotracheal tube.[8] Out of 17, the prognosis of 8 (47.05%) cases was reported to be fatal [Table 2]. These cases were presented to a health center in an advanced clinical course, and the majority of them had an underlying illness. The outcome of PAP is strongly determined by early detection, underlying conditions, and early WLL with bronchoscopy.[10,11] Recently, advanced treatment modalities such as the use of anti-inflammatory agents, WLL, immunomodulatory treatments, and lung transplants have shown some positive outcomes in a few case reports.

Since clinical features of PAP are indifferent and wide-ranging, missed and delayed diagnosis is common. The diagnosis of postnatal onset of PAP must be anticipated in every child with chronic respiratory distress and failure to thrive with diffuse alveolar infiltrate. The history of consanguineous parents needs to be ruled out for congenital PAP. Childhood PAP should be an integral part of clinical settings, and early detection and prompt treatment must be principal strategies to prevent further complications of PAP.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initial will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Iyengar JN, Reddy BK. Pulmonary alveolar proteinosis in children: An unusual presentation with significant clinical impact. Indian J Pathol Microbiol 2018;61:418-20.
2. Tabatabaei SA, Karimi A, Tabatabaei SR, Radpay B, Jadali F, Shiva F, *et al.* Pulmonary alveolar proteinosis in children: A case series. J Res Med Sci 2010;15:120-4.
3. Salvaterra E, Campo I. Pulmonary alveolar proteinosis: From classification to therapy. Breathe (Sheff) 2020;16:200018.
4. de Blic J. Pulmonary alveolar proteinosis in children. Paediatr Respir Rev 2004;5:316-22.
5. Latzin P, Tredano M, Wüst Y, de Blic J, Nicolai T, Bewig B, *et al.* Anti-GM-CSF antibodies in paediatric pulmonary alveolar proteinosis. Thorax 2005;60:39-44.
6. Verhasselt-Crinquette M, Franquet-Ansart H, Rakza T, Storme L, Copin MC, Devisme L. Congenital pulmonary alveolar proteinosis related to a surfactant protein B deficiency: Report of two cases. Ann Pathol 2009;29:481-4.
7. Hammami S, Harrathi K, Lajmi K, Hadded S, Ben Meriem C, Guédiche MN. Congenital pulmonary alveolar proteinosis. Case Rep Pediatr 2013;2013:764216.
8. Garg G, Sachdev A, Gupta D. Pulmonary alveolar proteinosis. Indian Pediatr 2009;46:521-3.
9. Al-Haidary AS, Alotaibi W, Alhaider SA, Al-Saleh S. A newly identified novel variant in the CSF2RA gene in a child with pulmonary alveolar proteinosis: A case report. J Med Case Rep 2017;11:122.
10. Zhang FZ, Yuan JX, Qin L, Tang LF. Pulmonary alveolar proteinosis due to *Pneumocystis carinii* in type 1 Hyper-IgM syndrome: A case report. Front Pediatr 2020;8:264.
11. Campo I, Luisetti M, Griese M, Trapnell BC, Bonella F, Grutters J, *et al.* Whole lung lavage therapy for pulmonary alveolar proteinosis: A global survey of current practices and procedures. Orphanet J Rare Dis 2016;11:115.